PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
E 2055 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06087	29/06/2000	29/06/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant FIDIA ADVANCED BIOPOLYMERS SRL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/01/2001	11.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Taylor, G.M. Telephone No. +49 89 2399 8406

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06087

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-29 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-14.

because:

☒ the said international application, or the said claims Nos. 4-6,12-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1,3 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☒ the claims, or said claims Nos. 1-14 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 7-11.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims

	No:	Claims	1-6,12-14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6,12-14
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III

1. No search report was established for the subject-matter of claims 7-11. Consequently, no opinion will be given on this subject-matter (Rule 66.1(e) PCT).

   Moreover, and as already stated during the search phase, support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small number of compounds/products within the scope of the present application, namely esters formed from alcohols. In fact, only one example is given which relates to the benzyl ester of hyaluronic acid.

   Thus, no opinion will be given on any subject-matter not adequately supported (Art. 34(4)(a)(ii) PCT).

   The expression "biomaterial" was also disregarded during search and the claimed scope in respect of this feature will not be addressed in this Opinion.

2. Claims 4-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

3. The subject-matter of claims 1-6 and 12-14 is not novel.

   Clinical Materials 1991, 8, 171 (**D1**), which is relevant for claims 1-4, 6 and 14, discloses the use of esters of hyaluronic acid, including the ethyl ester, for the treatment of wound healing in in vivo experiments, inter alia with respect to modification of the scarring process. The retardation of excess collagen formation was also observed (see Abstract, Introduction; Discussion).

   WO 99/04828 (**D2**), which is relevant for claims 1 and 2, discloses pharmaceutical compositions comprising hyaluronic acid esters, such as the benzyl ester (see Example 1).

   WO 97/07833 (**D3**), which is relevant for claims , discloses pharmaceutical

compositions comprising hyaluronic acid esters, such as the benzyl ester HYAFF 11 (see page 2, line 1-17; Examples; claims 1-28).

US-A-5 676 964 (**D4**), which is relevant for claims 1-6 and 12-14, discloses the use of the benzyl ester of hyaluronic acid for the treatment of scarring such as acne scars, post-surgical atropic irregularities and lacerated scars of the lip. See col. 16, lines 27-31; Example 41.

US-A-4 851 521 (**D5**), which is relevant for claims 1-6 and 12-14, discloses the use of hyaluronic acid esters, such as that derived from benzyl alcohol, for the same treatments as D4. See col. 48, lines 57-60; Example 24; col. 43, lines 40-4; claims 1, 5, 14.

Thus, the said claims do not meet the requirements of Art. 33(2) PCT

4. The subject-matter of claims 1-6 and 12-14 does not meet the requirements of Art. 33(3) PCT.

The use of hyaluronic acid esters, especially the benzyl ester HYAFF[SPEC0416] 11, for the treatment of scarring is known.

4.1 The addition of other active compounds cannot be seen as involving an inventive step, unless is gives rise to a surprising or unexpected effect. Thus, even if the optional components according to claims 3, 4 and 12 were explicitly included in the scope of a claim, no inventive step could be recognised.

Moreover, even in a case where a special effect can be shown, the effect must be credible over the whole range of the claimed subject-matter. In the case of present claims 3 and 4, it is extremely doubtful that the addition of "at least one additional pharmacologically or biologically active compound" would result in a beneficial effect. Even the range of substances given in claim 13 is extremely broad and highly unlikely to add a special effect over the whole of the claimed range.

4.2 The form of the medicament cannot be seen as providing an inventive step for the

subject-matter of the claims. Thus, claim 12 would only be seen as being inventive in conjunction with an inventive independent claim.

5. In the description, it is stated that hyaluronic acid derivatives are efficacious in reducing the extent of normotrophic scarring and that said activity is greater than hyaluronic acid itself (p. 5, lines 5-8). The specific example shown is that of benzyl hyaluronate in the form of HYAFF[SPEC0416] 11 (Example 1 and Figure 1).

It was already known that benzyl hyaluronate was known to have superior qualities from **Biomaterials 1996, 17, 1639** (**D6**). See the abstract; Tables 1 and 2; and Conclusions. However, this was not observed in relation to the treatment of scars or scarring.

The effect demonstrated for just a single application of HYAFF[SPEC0416] 11 versus a single application of hyaluronic acid (Figure 1) could be seen as being inventive. A claim restricted to the use of this composition would therefore appear to meet the requirements of Art. 33(3) PCT. However, the Applicant's attention is brought to the fact that Trademarks may not be used in the claims (PCT Guidelines C-III, 4.6a).

6. For the assessment of the present claims 4-6 and 12-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

7. Claims 1 and 3 are unclear because the definition of a "biomaterial" is unclear. Moreover, the distinction between a pharmaceutical composition or a biomaterial is unclear. In the context of said claims, there would appear to be no difference and as such, the expression "or biomaterial" has been disregarded for the

purposes of the Opinion.